

# Beriberi: Etiological and Clinical Considerations

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FOR some time prior to the abrupt descent of the Rising Sun on 15th August, 1945, and for one month after that event, the writer had the opportunity of observing beriberi among British and Australian troops in various Japanese prison camps in Malaya, Siam, and Burma. Sporadic beriberi was always with us, and two outbreaks were seen.

## ETIOLOGY.

Beriberi was recognised by the Chinese 3000 B.C. The etiology, however, remained obscure till 1870. In that year Eijkman, working in Java, noted an epidemic of paralysis among fowls fed on polished rice. He found that this polyneuritis gallinarum could be cured if an extract of rice polishings were added to the diet. That polyneuritis gallinarum corresponded to human beriberi was shown by Frazer and Stanton in 1910. These investigators produced beriberi in convicts by feeding them a diet consisting solely of overmilled rice. They also succeeded in curing the disease by adding rice polishings to the diet. Frazer and Stanton concluded that the pericarp aleurone layers and the embryo of grain which are removed in the production of polished rice contained an anti-beriberi substance.

The chemical composition of this substance was determined by Williams in 1935, and it was eventually synthesised by Williams and Spies in 1938. It was found to be a compound of pyrimidine and thiazole, to which Williams gave the name thiamin.

Beriberi was therefore defined as a disease resulting from a metabolic disturbance caused by deficiency of the ante-neuritic vitamin  $B_1$ , or thiamin. The minimal daily requirements of thiamin are in the region of 1 mg. or 333 I.U.

Recently, however, it has been recognised that factors in addition to thiamin deficiency are concerned in the production of beriberi. It has been observed that beriberi is an uncommon complication of simple starvation. The disease was rarely seen among the starving populations of Europe during the war. Beriberi complicating anorexia nervosa has only once been recorded.

The question of additional factors has been investigated by Cowgill in 1934 and by Williams and Spies in 1938. Cowgill as a result of his investigations came to the conclusion that the incidence of the disease was related to the ratio between the thiamin and the caloric value of the diet, rather than to the daily intake of thiamin. Williams and Spies attacked the problem by analysing typical Occidental and Oriental diets. They found that the differences in thiamin value was insufficient to explain the rarity of the occurrence of beriberi in association with the former diet and its frequency in association with the latter. They noted that the chief difference in the diets was the greater fat-content of the American diet. From this they concluded that fat had a  $B_1$  sparing action. Analytically it was shown that the best index of the liability of a diet to produce beriberi was the relationship between the thiamin and the non-fat caloric value. This they express as the

T/N.F.C. ratio, where N.F.C. represents the daily calories derived from food other than fats, and T the daily thiamin content of the diet in micrograms. They noted that T/N.F.C. below .3 was indicative of a beriberi-producing diet.

These facts were substantiated by experience in Japanese prison camps.

The diet analysis shown of the period March-July, 1945, indicates that the daily thiamin intake was on an average little greater than one-third of the normal daily requirements. Yet on this diet rather less than 10 per cent. of the prisoners showed clinical evidence of beriberi.

The explanation is that the very low thiamin intake was associated with a low caloric intake, consequently the thiamin/fat calorie ratio did not fall much below the critical figure .3.

Within a few days of the capitulation of the Japanese on 15th August, 1945, the daily ration was increased by the addition of 4 oz. of rice and 2 oz. of protein. The thiamin content of the diet remained unaltered. Calculation shows that these additions to the diet cause the T/N.F.C. ratio to fall to a figure of .204. Beriberi was therefore to be expected, and an outbreak appeared toward the end of August. The short interval, fourteen days, as opposed to the ninety days dietetic imbalance commonly required to produce beriberi, is explicable on the grounds that prior to the change in diet the prisoners had lived on the beriberi threshold T/N.F.C. ratio just below .3.

#### CLINICAL FINDINGS.

##### *Sporadic Beriberi.*

As a sporadic occurrence, beriberi affected some five to fifteen per cent. of the prisoners in Japanese prison camps. Three types of the disease are described and were seen—

- (a) Neuritic.
- (b) Oedematous.
- (c) Cardiac.

Isolated involvement of the cardio-vascular or nervous system was infrequent. Oedema was, however, often the only manifestation.

##### *Neuritic Beriberi.*

The neuritic manifestations were similar to those of multiple neuritis of other origin. The degenerative lesions showed a predilection of the long nerves, so that wrist-drop and foot-drop were frequently seen. The anterior crural nerves were involved early, with usually weakness and wasting of the quadriceps extensor, leading to inability to rise from the squatting position. Inability to rise from the squatting position—a positive “squatting test”—was sometimes the first sign of beriberi. Occasionally the presenting symptom was hoarseness, due to involvement of the recurrent laryngeal nerve in the degenerative process.

The motor manifestations were usually preceded by the sensory symptoms of peripheral neuritis. There were complaints of numbness and tingling, particularly in the hands and feet and along the inner sides of the thighs.

Examination of sensory function showed a varying degree of impairment of superficial sensation. The areas most commonly affected were the distal parts of

the limbs and the inner sides of the thighs. The affected muscles were painful on deep pressure and the tendo Achilles usually insensitive.

The weak muscles—quadriceps, dorsiflexors of the feet, and extensors of the wrist—usually showed some degree of wasting. The tendon jerks were diminished or absent in the affected limbs.

Marked neuritic manifestations were almost invariably accompanied by cardiovascular abnormalities. The commonest were (1) Persistent tachycardia; (2) Marked fall in blood pressure—systolic readings below 100 and diastolic readings below 60 were frequent; (3) Cardiac enlargement—usually slight in the absence of œdema.

#### *Oedematous Beriberi.*

A slight puffiness of the face and pitting œdema of the lower limbs below the knees were the most frequent manifestations of sporadic beriberi. Oedema of this degree was not usually accompanied by evidence of involvement of the cardiovascular or nervous systems.

Massive œdema associated with cardiac failure—a common feature in one outbreak—was infrequent as a sporadic manifestation.

The following case showed a combination of the œdematous and neuritic types.

PRE. T., 7TH COAST REGT. R.A., admitted 23/8/45.

*History.*—For two years he has suffered from—

1. Periodic swelling of the face, and of the legs below the knees.
2. Numbness and tingling in the hands and feet.
3. Severe cramp-like pains in the muscles of the lower limbs.

*Examination.*—Marked wasting. Weight 9 st. 7 lb. Normal weight 13 st. 6 lb. No gross anæmia. There is pitting œdema of the lower limbs below the mid tibia. *Heart and lungs:* No clinical or radiological abnormality. *Abdomen:* Liver not enlarged. Spleen just palpable. *C.N.S.:* Positive findings—Impairment of all forms of superficial sensation in lower limbs below the knee-joints and along the medial aspect of the thighs. Marked tenderness in the muscles of the calves. Wasting of the quadriceps extensors. Squatting test positive. Slight weakness of the dorsiflexors of the ankles.

#### OUTBREAKS OF BERIBERI.

Two outbreaks of the disease were seen. Each presented unusual features.

Outbreak No. 1 was seen among those personnel of the ill-fated “F” Force who had survived the “death” march through Siam to the Burma border in 1943.

For many reasons, including the complete absence of paper, clinical records of this epidemic are not available. The striking feature was the high incidence of cardiac manifestations of the disease. Grave cardiac involvement appeared as—

- (1) Acute cardiac beriberi.
- (2) Congestive cardiac failure.
- (3) Major conduction defects terminating in Stokes-Adams syndrome.

#### *Acute Cardiac Beriberi:*

Known by the Japanese as *shōshin*. Men apparently well or suffering from œdematous beriberi of moderate or mild degree would collapse at work with acute

pain in the chest. Death as a rule rapidly followed. When seen before death, they showed extreme dyspnoea, restlessness, cyanosis, and distention of the jugular veins. They complained of unbearable pain in the chest, radiating into the neck and arms. Clinical evidence of cardiac enlargement both to right and left was usually easily elicited. The heart-sounds were faint, distant, and tic tac in character. Intravenous administration of thiamin (when the drug was available) produced dramatic relief. In its absence, these men invariably died.

#### *Congestive Cardiac Failure.*

The features did not differ markedly from the congestive failures produced by the more common causes. Oedema partly of cardiac origin was as a rule generalised, involving limbs, trunk, and face. In the terminal stages these men were orthopnoeic and cyanotic, with distended, pulsating jugular veins. The heart was always markedly enlarged, the sounds faint and tic tac in character. The first heart-sound heard over the displaced apex was frequently split. Signs of bilateral pleural effusion could be elicited. The liver was enlarged and the abdomen contained free fluid. Infection of the oedematous subcutaneous tissues, resulting in widespread cellulitis, often occurred preterminally.

#### *Conduction Defects.*

Evidence of defective conduction in association with beriberi is of interest, since this finding is contrary to that of the leading authorities on the subject—Wenckebach (1928), Weiss (1940). We regarded splitting of the cardiac first sound as the earliest evidence of a conduction defect. Apart from this, cases were seen to progress through the stage of partial to complete heart-block and to terminate during their first or subsequent attack of typical Stokes-Adams syndrome.

It may be argued that since most of the men suffered from uncontrolled malaria and many were convalescent from cholera, in the production of the bundle damage some other factor was at work, such as the toxin of the malarial parasite or that of the cholera vibrio. These toxins may have been contributing factors.

Two observations, however, indicated that beriberi was the main factor :

- (1) Gross conduction defects associated with Stokes-Adams syndrome did not occur in the absence of other signs of beriberi, either oedematous or neuritic.
- (2) Thiamin, in the isolated case in which its effect was observed, rapidly brought about a return of normal conduction.

The case remembered is that of a R.A.M.C. staff-sergeant who while recovering from the congestive failure of beriberi developed bradycardia (P.R. 36) and Stokes-Adams attacks. He had some ten attacks in six days. 20 mg. of thiamin were then given intravenously, followed by 5 mg. daily for one week, after which the supply of the drug failed. Twenty-four hours after the initial dose the pulse-rate was normal; however, ten days after the drug was stopped, bradycardia and Stokes-Adams attacks reappeared. No attacks occurred while thiamin was given.

#### OUTBREAK No. 2.

This outbreak appeared toward the end of August, 1945, following an increase in the ration and upset of the thiamin non-fat calorie ratio of the diet. The mani-

festations were mainly œdematous. Some cases, however, showed a syndrome which, as far as can be ascertained from the literature available, has not previously received attention. The characteristics of this syndrome were :

- (1) Acute generalised non-pitting œdema.
- (2) Hypertension.
- (3) Fairly rapid response of both œdema and hypertension to the parenteral administration of thiamin.

#### CASE REPORTS.

*Case I*—Pte. Z., 2/26 Bn. A.I.F. Admitted 23/8/45.

*Previous Illnesses.*—Amœbic dysentery, 1943; Malaria B.T., twenty attacks.

*History of Complaint.*—Since June, 1943, he has suffered from painful feet, cramps in the calves of the legs, and occasional swelling of the feet and ankles.

Four days prior to admission he has been passing less urine than usual. Three days before admission his face became swollen, and the day before admission he noticed that his "body became swollen all over." He had suffered from headaches and loss of appetite for ten days.

*Examination.*—Oedema involves the face, trunk, limbs, and genitals. Pitting can not be demonstrated. There is no cyanosis or distension of the jugular veins. *C.V.S.:* Heart: no clinical enlargement. Heart-sounds normal. B.P. 190/130. *Lungs:* N.A.D. *Abdomen:* Liver not enlarged. Spleen just palpable. *C.N.S.:* There is no muscle weakness or wasting and no sensory loss. The tendon jerks are present. Urine N.A.D.

*Treatment.*—Thiamin 50 mg. intravenously, followed by 50 mg. by intramuscular injection daily. Fluids restricted. No salt.

*Response.*—A rapid diuresis ensued. During the forty-eight hours following the commencement of treatment 418 oz. urine were passed. Oedema rapidly subsided. Five days after admission there remained only slight puffing of the face and ankles.

*Blood Pressure.*—Ten days after admission 140/90.

*Case II*—Pte. S., 2/30th Bn. A.I.F. Admitted 27/8/45.

*Previous Illnesses.*—Malaria B.T. at monthly intervals since 1942. No previous beriberi.

*History.*—During the past week he has been passing very little urine. Four days before admission, on waking he noticed his face swollen; swelling of the genitals then appeared, and gradually the swelling involved the trunk and limbs.

*Examination.*—Oedema involves the face, trunk, and limbs. There is no pitting. There is no dyspnoea, cyanosis, or distention of the jugular veins. *C.V.S.:* Heart: Not clinically enlarged. Heart sounds are hyperactive, but otherwise normal. B.P. 200/114. *Lungs:* N.A.D. *Abdomen:* Liver not enlarged. Spleen just palpable. *C.N.S.:* No sensory or motor abnormality. Tendon jerks present. *Urine:* N.A.D.

*Treatment.*—Thiamin 50 mg. I.V., followed by 50 mg. I.M. daily.

Fluid restriction. No salt.

*Response.*—A diuresis was established in four days. Seven days after commencement of treatment the oedema had gone. Fourteen days after admission the blood pressure had fallen to 160/100.

*Case III*—Pte. P., 2/20th Bn. A.I.F. Admitted 31/8/45.

This case showed, in addition to non-pitting oedema, hypertension syndrome, cardiac manifestations reminiscent of those seen in the first outbreak.

*Previous Illnesses.*—Malaria B.T. twenty attacks; Malaria M.T., two attacks; Bacillary Dysentery, two attacks.

*History.*—He noticed swelling of the lower limbs four days prior to admission. This swelling gradually spread upwards, and soon the whole body became swollen. A severe continuous headache has been present since the appearance of this oedema.

On the evening prior to admission while lifting a bucket full of water he had a sudden severe pain in his chest and collapsed. Thiamin 50 mg., given intravenously by his unit medical officer, relieved the acute pain. He still complained of a feeling of tightness in his chest.

*Examination.*—A non-pitting oedema involves the face, thighs, limbs, and genitals. *Heart:* No clinical enlargement. Heart-sounds faint and tic-tac in character. Frequent extra systoles. B.P. 150/100. *Lungs and Abdomen:* N.A.D. *C.N.S.:* Impaired superficial sensation in the lower limbs below the knees. No other abnormality. *Urine:* N.A.D.

*Treatment.*—After an initial injection of 50 mg. of thiamin intravenously, 50 mg. were given daily by intramuscular injection. Oedema had completely gone by the fourth day after the commencement of treatment; tightness and discomfort in the chest disappeared. One week after admission his B.P. had fallen to 130/64. The heart-sounds were still tic-tac, but the extra systoles had gone.

#### DISCUSSION.

Vitamin B<sub>1</sub>, when absorbed, combines with pyrophosphoric acid to form thiamin pyrophosphate or co-carboxylase. Co-carboxylase is the enzyme essential for a vital stage in the oxidation of glucose by living cells. In its absence the breakdown of glucose is arrested at the pyruvic acid stage. Since nerve tissue depends almost entirely on the oxidation of glucose for its metabolism, the frequency of degenerative changes in the nervous system is explicable.

The involvement of the heart in the disease process is, however, less easily explicable. The finding at post-mortem is marked hypertrophy and dilatation of the right side of the heart.

Wenckebach assumes that the heart as a whole fails. The signs of right-sided failure and the marked dilatation of the right side of the heart found at post-mortem he explains on a purely mechanical basis: "In cases of increasing insufficiency of the whole heart, the right heart is doomed to suffer much more than the left side, even to suffer to the profit of the latter." The failure and hypertrophy

of the right heart he attributes to imbibition of fluid by the muscle-fibre. He offers no explanation as to why the hypertrophy of muscle-fibres produced by imbibition of fluid should be confined to the right side of the heart.

Whether or not the heart-muscle in beriberi imbibed fluid might be determined by comparing the weight of dried beriberi hearts with the weight of dried normal hearts. There is no record of this experiment having been performed in human beriberi. It has, however, been performed on pigeons. Newcomb (1930) found that the enlarged hearts of pigeons suffering from beriberi showed no abnormal water content.

That the disordered metabolism of beriberi might lead to the accumulation in the blood of metabolites having a toxic action on the myocardium must be considered. There is evidence pointing to such an accumulation. It is known that the blood pyruvic acid is high in beriberi, often reaching a figure of 2 mg./100 c.c. (normal .5 mg.) Lee and Platt (1938) have shown that in  $B_1$  deficient states moderate exercise is followed by a marked rise in the blood pyruvate, whereas the normal subject must be exercised to exhaustion before any appreciable rise occurs. They further showed that the time required for the removal of the excess pyruvate is greater than normal.

Inawashiro and Hayasaka have noted a similar rise in the blood lactic acid and a delay in its removal.

Our experience showed that the cardiac manifestations of beriberi were related to muscular activity.

Thus, the first outbreak of the disease in which grave cardiac involvement was so frequent occurred among troops who had just completed a long and exhausting jungle march, and who at the time of development of the outbreak were working as slave labour on the Burma railway. Again, acute cardiac beriberi—shôshin—appeared while the individual was engaged in some strenuous muscular effort.

These findings would indicate that possibly pyruvic acid and lactic acid had a toxic action on the myocardium. Haynes and Weiss have failed to produce any toxic effect by injecting these acids into  $B_1$  deficient animals. The toxic factor may, however, be a metabolite closely associated with pyruvic acid and lactic acid.

The occurrence of conduction defects must be regarded as unusual.

Aslmeier found that even in the worst conditions of failure "the beriberi heart gave a perfectly normal electro-cardiograph without arrhythmia, extra systoles, heterotopic rhythms, or disturbances of conduction in the bundle or in the conducting fibres of the ventricles."

Wenckebach stresses the contrast between the weakened muscle and an undisturbed or accelerated conduction. He uses this as an argument in favour of the theory of imbibition of fluid by the muscle-fibre, since it has been shown by Engelmann that the frog's heart immersed in water lost the power of contraction without disturbance of conductivity, and by De Boer that the human heart behaved in a similar manner.

Weiss reported the electro-cardiographic changes in two white men suffering from beriberi. In neither was there pathological prolongation of the P.R. interval.

Weiss et al. studied the electro-cardiographic changes in thiamin-deficient dogs. Changes were found in the T-waves and S.T. segments. Prolongation of the P.R. interval was not a feature.

Carter and Dury have, however, succeeded in producing heart-block in rice-fed pigeons. It would appear, therefore, that the effect of thiamin-deficiency on the animal heart required further investigation.

The nature of the œdema and the mechanism of its production in beriberi remain obscure. In most cases it occurred first in the dependent parts and pitted easily. On incision, the subcutaneous tissues serous fluid escaped. These features would indicate an extra cellular location in the tissues and a similarity to cardiac œdema. Many sporadic cases of beriberi, however, showed no cardio-vascular abnormality. The generalised distribution and absence of pitting of the œdema seen during the second outbreak suggested that it was at least partly intracellular. The association of this type of œdema with hypertension is of interest. Hypertension has not, as far as can be ascertained, been previously recorded in connection with beriberi. All authorities on the disease emphasise the lowering of the blood pressure which occurs, in particular the lowering of the diastolic pressure.

It is suggested that those showing the generalised non-pitting œdema hypertension syndrome produce as a result of their disturbance metabolism, a metabolite causing an increase in intracellular osmotic pressure, resulting in imbibition of fluid by the cell. An intracellular œdema affecting renal tissue might lead to renal ischæmia and hypertension.

#### SUMMARY.

Sporadic cases and outbreaks of beriberi among prisoners of war are described. Evidence is presented in favour of the operation of factors in addition to thiamin-deficiency in the production of the disease.

An unusual beriberi syndrome is described.

The occurrence of heart-block in association with beriberi is recorded.

#### DIET ANALYSIS

MARCH—JULY, 1945.

Prison of War Camp, Changi, Singapore.

MARCH		C.		P.		F.		CAL.		N.F.C.		T.		T/N.F.C.
H.	-	306	...	36	...	56	...	1,800	...		...	370	...	.26
L.	-	260	...	38	...	50	...	1,560	...		...	335	...	.3
APRIL														
H.	-	350	...	45	...	67	...	2,100	...	1,418	...	450	...	.31
M	-	250	...	41	...	61	...	1,700	...	1,210	...	390	...	.33
L.	-	210	...	40	...	61	...	1,500	...	970	...	382	...	.4
MAY														
H.	-	350	...	44	...	65	...	2,244	...	1,595	...	480	...	.31
M.	-	280	...	41	...	58	...	1,876	...	1,280	...	420	...	.32
L.	-	238	...	39	...	58	...	1,690	...	1,100	...	403	...	.4

# JUNE

H.	-	312	...	46	...	63	...	2,041	...	1,442	...	386	...	.27
M.	-	255	...	43	...	57	...	1,731	...	1,206	...	315	...	.26
L.	-	213	...	41	...	57	...	1,559	...	1,016	...	327	...	.32

# JULY

H.	-	318	...	34	...	57	...	1,973	...	1,444	...	410	...	.28
M.	-	245	...	30	...	51	...	1,602	...	1,129	...	328	...	.29
L.	-	205	...	27	...	51	...	1,425	...	956	...	303	...	.32

C.—Carbohydrate.

P.—Protein.

F.—Fat.

Cal.—Calorie value.

N.F.C.—Non-fat calorie.

T.—Thiamin in micrograms.

T/N.F.C.—Thiamin/non-fat calorie.

SCALES OF RATINGS.

H.—High.

M.—Medium.

L.—Low.

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## REVIEW

THE CIRCULATION IN THE FŒTUS. By Kenneth J. Franklin, D.M., F.R.C.P., Alfred E. Barclay, O.B.E., D.M., F.R.C.P., F.F.R., F.A.C.R., and Marjorie M. L. Pritchard, M.A. Pp. 28. Blackwell Scientific Publications. 2s. 6d.

THIS short monograph is a synopsis by Dr. K. J. Franklin of the book on the foetal circulation and cardio-vascular system by the same author and his colleagues at the Nuffield Institute in Oxford.

A brief historical review is given of the advances made in the knowledge of the foetal circulation since Galen, in the second century A.D., described the foramen ovale. This is followed by an account of the conclusions reached from observations made on foetal lambs with the aid of cine-radiographic apparatus. The text is well illustrated by X-ray photographs, obtained after the injection of radio-opaque substances into the blood stream.

As the author states, much research remains to be done along these lines, and further publications will be awaited with interest. This pamphlet will well repay the attention of senior students of biology and is moderately priced.

J. W. M.